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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/025,222	PELLETIER ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *66,72,86-88,91 and 105-108* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *88,105 and 106* is/are allowed.

6)☒ Claim(s) *66,72,86,87,91,107 and 108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] The finality of the rejection of the last Office action is withdrawn. According to MPEP 706.07(d), "if ... the primary examiner finds the final rejection to have been premature, he or she should withdraw the finality of the rejection." While there are no new rejections raised in the instant Office action, it is the examiner's position that the finality of the last Office action is premature as the examiner has presented substantially new reasoning in maintaining the scope of enablement rejection. In order that the issues presented by the examiner may be fully developed in the prosecution record, the instant Office action is a non-final Office action.

[2] Applicants' amendment to the claims, filed 1/28/2005, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

Claim Objections

[3] The objection to claim 106 as being a substantial duplicate of claim 71 is withdrawn in view of applicants' cancellation of claim 71.

[4] The objection to claim 88 as being a substantial duplicate of claim 105 is withdrawn in view of applicants' amendment to claim 88.

Claim Rejections – 35 USC § 112, First Paragraph

[5] The written description rejection of claim 72 under 35 U.S.C. 112, first paragraph, is withdrawn upon further consideration.

The court in *UC California v. Eli Lilly*, (43 USPQ2d 1398) held that "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." In this case, the specification discloses SEQ ID NO:2 and C-terminal fragments thereof that bind to SEQ ID NO:4. It is the examiner's position that this is not a representative number of species of the genus sufficient to describe all members of the genus. The examiner notes that the genus of polypeptides comprising SEQ ID NO:6 encompasses species that are widely variant with respect to their structures, *i.e.,* the genus encompasses members with any additional amino acids at the N- or C-terminus of SEQ ID NO:6, including full length polypeptides that can have, in addition to the ability to bind SEQ ID NO:4, any additional biological activity or activities or no function at all. It is the examiner's position that the genus is not described by a representative number of species of polypeptides comprising SEQ ID NO:6. However, the genus appears to be fully described by recitation of a structural feature common to the members of the genus (SEQ ID NO:6), which feature constitutes a substantial portion of the genus. In this case, all members of the genus of recited first polypeptides comprising SEQ ID NO:6 have a common structural element, *i.e.,* the polypeptide of SEQ ID NO:6 (amino acids 561 to 599 of SEQ ID NO:2). The court in *UC California v. Eli Lilly* did not elaborate on what structural feature constitutes a "substantial portion of the genus." However, as the presence of SEQ ID NO:6 is sufficient to confer binding to SEQ ID NO:4 (at least at the C-terminus

of SEQ ID NO:2), this structural element is considered by the examiner to be a substantial portion of the genus of polypeptides comprising SEQ ID NO:6.

[6] Upon further consideration of the claims, the scope of enablement rejection of claim 106 under 35 U.S.C. 112, first paragraph, is withdrawn for the following reasons.

The recited fragment of SEQ ID NO:2 is limited to amino acids 229-599 or amino acids 380 to 599 of SEQ ID NO:2. It is the examiner's position that it would not require undue experimentation to make and use the a polypeptide consisting of amino acids 229 to 599 or amino acids 380 to 599 of SEQ ID NO:2.

[7] The scope of enablement rejection of claims 66, 72, 86-87, 91, and 107-108 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record and for the reasons stated below.

The polypeptide of SEQ ID NO:2 is disclosed in the specification (Example 2, pp. 97-102) as being isolated from *Staphylococcus aureus* (*S. aureus*), which is a known pathogenic bacterium (see Harbarth et al., cited as A20 in the IDS filed 12/23/2001). The specification discloses that the expression of a bacteriophage polypeptide, SEQ ID NO:4, using *S. aureus* as a host has an inhibitory effect on the growth of *S. aureus* (see pp. 96-97 of the specification). The specification goes on to disclose that SEQ ID NO:4 was shown to bind to SEQ ID NO:2 and fragments thereof (see Examples 3-4 pp. 102-109). While the specification does not elaborate on the mechanism by which expression of SEQ ID NO:4 in an *S. aureus* host results in inhibition of the *S. aureus* host's growth, the inference is that binding of SEQ ID NO:4 to SEQ ID NO:2 inhibits the growth of *S. aureus*.

The specification asserts SEQ ID NO:2 has primase enzymatic activity based on sequence similarity to an *S. aureus* primase (see p. 101, bottom and Figure 7B) and other bacterial primases (p. 102, middle and Figure 7B). While there is no dispute that SEQ ID NO:2 shares sequence similarity with other primase polypeptides, the specification fails to demonstrate that SEQ ID NO:2 has primase activity, *e.g.,* by an activity assay, or fails to provide evidence that SEQ ID NO:2 has primase activity, *e.g.,* identification of key residues that impart primase activity. Functional assignment of a polypeptide based solely on similarities between two amino acid sequences is known in the prior art to be unpredictable. For example, the prior art acknowledges that polypeptides that share structural similarity to other polypeptides do not necessarily share identical functions (see, *e.g.,* Scott et al. *Nat Genet* 21:440-443 and Brenner *Trends Genet* 15:132-133). While sequence similarities can be used to *predict* a protein's function, such evidence cannot substitute for empirical evidence showing the activity of a polypeptide, *e.g.,* activity assays or identification of key residues in a polypeptide's active site that confer a particular enzymatic activity, *e.g.,* amino acids involved in the catalytic triad of a serine protease. In this case, it is just as likely that SEQ ID NO:2 is a non-functional mutant.

The specification asserts the utility of the polypeptide of SEQ ID NO:2 is for "screening and identification of anti-bacterial agents and more particularly for anti *S. aureus* agents" (p. 109, lines 14-18). However, there is no evidence of record that suggests that inhibiting the asserted primase activity of SEQ ID NO:2 has a negative effect on the growth of *S. aureus.* The evidence of record only shows that expression of

SEQ ID NO:4 in an *S. aureus* host inhibits growth of the host. It is the examiner's position that the asserted utility for SEQ ID NO:2 as being used in the "screening and identification of anti-bacterial agents and more particularly for anti *S. aureus* agents" is not substantial at least because: 1) the specification fails to demonstrate that SEQ ID NO:2 has primase activity and 2) even assuming *arguendo* SEQ ID NO:2 has primase activity, the specification fails to demonstrate that the activity of SEQ ID NO:2 is required for growth of *S. aureus*. Further experimentation is required to determine whether SEQ ID NO:2 has primase activity and is required for growth of *S. aureus*. This type of utility is not considered a "substantial utility". See e.g., *Brenner v. Manson,* 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). The specification must teach a skilled artisan how to use what is claimed and not merely provide a blueprint for further experimentation in order for an artisan to identify a use for the claimed invention.

While the specification fails to provide evidence that SEQ ID NO:2 has primase activity and further fails to disclose that inhibition of SEQ ID NO:2 can result in inhibition of *S. aureus* growth, it is the examiner's position that the claimed polypeptide or composition has a specific and substantial utility for the following reasons. First, the polypeptide of SEQ ID NO:2 can be used to generate antibodies to screen for the presence of *S. aureus,* particularly as there is no evidence of record that the polypeptide of SEQ ID NO:2 occurs in other bacteria and would appear to be specific for *S. aureus,* particularly the conserved C-terminal end of SEQ ID NO:2, which is identical in other *S. aureus* polypeptides presumed to have primase activity (see O'Donnell et al. and Benton et al., cited in the Office action mailed 6/1/2004). Second, the polypeptide of

SEQ ID NO:2 and fragments thereof comprising SEQ ID NO:6 can be used to purify the polypeptide of SEQ ID NO:4. The use of SEQ ID NO:2 and C-terminal fragments thereof for affinity purification of SEQ ID NO:4 is a specific and substantial utility as the specification discloses a correlation between the expression of the polypeptide of SEQ ID NO:4 and the inhibition of *S. aureus* growth.

RESPONSE TO ARGUMENT: Addressing claims 66 and 72, applicants argue the claims are directed to a well-defined group of polypeptides having shared structure and function. According to applicants, a skilled artisan would understand the scope of claimed polypeptides and, using the specification for guidance, would be able to easily make and use a polypeptide encompassed by the scope of the claims. Applicants argue the examiner "appears to be addressing the invention from the standpoint of one starting from 'scratch.'" According to applicants, a skilled artisan having knowledge that the amino acid sequence of SEQ ID NO:6 imparts the ability of a polypeptide to bind SEQ ID NO:4 can make other polypeptides that fall within the scope of the claims and test those polypeptides for the ability to bind SEQ ID NO:4 by methods disclosed in the specification without requiring undue experimentation.

Applicants' argument is not found persuasive. The examiner acknowledges applicants' disclosure of SEQ ID NO:6 as a C-terminal fragment of SEQ ID NO:2 that imparts binding of SEQ ID NO:2 to SEQ ID NO:4. There is no dispute that placing this fragment at the C-terminus of other polypeptides also likely imparts the ability of the other polypeptides to bind SEQ ID NO:4. However, the examiner maintains the position that making the full scope of claimed polypeptides (claim 66) or compositions (claim 72)

would require undue experimentation. According to applicants, the specification discloses several fragments of SEQ ID NO:2 (Figure 10) and a fusion protein comprising GST fused to SEQ ID NO:2 (pp. 105-109 of the specification) as working examples of the claimed polypeptides. However, it is noted that these working examples are all limited to having SEQ ID NO:6 localized at the C-terminus of the respective polypeptide. As stated in a previous Office action, there is no evidence of record that a polypeptide having an internal amino acid sequence of SEQ ID NO:6, *e.g.,* SEQ ID NO:6 with 100 additional amino acids at the N- and C-terminal ends, would have the ability to bind SEQ ID NO:4. It is well known in the art that the amino acid sequence of a protein determines its fold, *i.e.,* shape (see The "Encyclopedia of Molecular Biology" Creighton, T., John Wiley and Sons, Inc. New York, 1999, pp. 1994 and 2020). The ability of a polypeptide to bind a cognate polypeptide is dependent upon its shape and the shape of the binding partner (The "Encyclopedia of Molecular Biology," pp. 2027-2033). Alterations to a polypeptide's sequence result in alterations of the shape of the polypeptide and consequently, the ability to bind to other polypeptides (The "Encyclopedia of Molecular Biology," pp. 2032-2033). With the exception of polypeptides having SEQ ID NO:6 at their C-terminal end, the specification provides no guidance as to those polypeptides that comprise SEQ ID NO:6 that are likely or not to bind SEQ ID NO:4.

In a previous Office action, the examiner likened the interaction of SEQ ID NO:6 and SEQ ID NO:4 to an antibody-antigen protein interaction, which is a common type of protein-protein interaction (The "Encyclopedia of Molecular Biology," p. 2027 and

Buckingham, 4th Horizon Symposium, "Picking the Pockets of Protein-Protein Interactions, April 2004, pp. 1-4, particularly p. 1, left column). The examiner cited the reference of Abaza et al. (see Office action mailed 10/28/2004), which provides evidence that altering the amino acid sequence outside of an antibody binding domain, *e.g.,* by mutating amino acids outside of an antigenic region, can significantly affect protein-protein interaction. Applicants do not dispute this evidence. In view of this evidence, it is highly unpredictable as to the ability of all polypeptides comprising SEQ ID NO:6, *e.g.,* a polypeptide having 100 amino acids at the N- and C-terminal ends of SEQ ID NO:6, to bind SEQ ID NO:4.

Also, it is noted that the primase polypeptides of SEQ ID NO:2 and O'Donnell et al. and the primase polypeptide encoded by the nucleic acid of Benton et al. (cited in the Office action mailed 6/1/2004) all have the sequence of SEQ ID NO:6 located at their *C-terminal ends.* As the three structurally distinct primase polypeptides all have an identical C-terminal sequence, this certainly suggests that the presence of this sequence at their respective C-terminal ends is structurally important.

In this case, the specification fails to provide even a single working example of a polypeptide having an internalized sequence of SEQ ID NO:6 that is able to bind SEQ ID NO:4. Also, the specification fails to provide any objective evidence that SEQ ID NO:6 having additional amino acids, particularly at its C-terminus, would maintain the ability to bind SEQ ID NO:4. As such, one of skill in the art has no expectation that a polypeptide comprising SEQ ID NO:6 having additional amino acids at the C-terminal end thereof, would have the ability to bind SEQ ID NO:4. Aside from fragments of SEQ

ID NO:2, the specification fails to provide guidance regarding those polypeptides comprising SEQ ID NO:6 that are likely to bind SEQ ID NO:4. As noted above, in view of the evidence of Abaza et al., it is highly unpredictable as to whether a polypeptide having an internal amino acid sequence of SEQ ID NO:6 would bind to SEQ ID NO:4. As such, one must screen the vast number of polypeptides that *comprise* SEQ ID NO:6 including all sequences having any additional amino acids, particularly at the C-terminus of SEQ ID NO:6, by a trial and error process for those that have the desired activity/utility. Such experimentation was not routine at the time of the invention.

Addressing claims 86-87, 91, and 107-108, applicants argue the claims are directed to a well-defined group of polypeptides having shared structure and function and, according to applicants, it would not require undue experimentation for a skilled artisan to make and use the claimed invention. Applicants note Example 14 of the Revised Interim Written Description Guidelines Training Materials approvingly cites a claim reciting variants of a sequence identifier (SEQ ID NO:3) having 95% identity and a recited function, which, according to applicants is analogous to the instant claims. Applicants assert that from the analysis of the claim in Example 14, the PTO views claims to polypeptide variants having at least 95% identity to be fully enabled and that it follows that the instant claims are fully enabled.

Applicants' argument is not found persuasive. The examiner maintains the position that undue experimentation is required to make the broad scope of polypeptides as encompassed by the claims. While applicants attempt to relate the instant claims to the claim of Example 14 of the Revised Interim Written Description

Guidelines Training Materials, Example 14 is inapposite to the claims of the instant application at least the following reasons. MPEP 2161 states, "[t]he written description requirement is separate and distinct from the enablement requirement." As such, claims that meet the written description requirement of 35 USC 112, first paragraph, do not necessarily satisfy the enablement requirement of that statute. Second, it is noted that the specification in Example 14 disclosed a liver protein that catalyzes a reaction. In this case, there is no evidence of record that the polypeptide of SEQ ID NO:2 catalyzes any reaction.

Also, the examiner disagrees with applicants' argument that the "PTO views claims to polypeptides and their variants (having at least 95% identity), that include a recitation of activity, to be fully enabled." First, it is noted that the PTO has provided no indication, positive or negative, of an enabling disclosure for the claimed variants in Example 14 of the Written Description Guidelines. Such an analysis is fact-based and cannot be made *a priori.* There is no dispute that procedures for making variants of a polypeptide and an assay for measuring binding activity or primase activity were known in the art at the time of the invention. However, that these methods were known in the art at the time of the invention does not necessarily provide a positive indication of an enabling disclosure and in this case it does not.

Regarding claims 86-87, as with claims 66 and 72, the claimed polypeptides are limited to those that bind SEQ ID NO:4. However, in contrast to the polypeptides of claims 66 and 72, the polypeptides of claims 86-87 are not required to at least having SEQ ID NO:6. Thus, a skilled artisan must, without any guidance provided in the

specification or prior art, determine, by a trial and error process, which of those variants of SEQ ID NO:2, including single amino acid substitution, insertion, and deletion and combinations of amino acid substitution(s), insertion(s), deletion(s), and addition(s) within the identity or similarity limitations will generate a polypeptide having the desired binding activity. As evidenced by Abaza et al., Colman et al. (cited in the Office action mailed 10/28/2004), and Branden et al. (cited in the Office action mailed 1/5/2004), the effects of such amino acid alterations are highly unpredictable.

Regarding claims 91 and 107-108, while the scope of the claims is limited to polypeptides having a recited biological activity, *e.g.,* RNA primase activity, there is no evidence of record that SEQ ID NO:2 exhibits any of the asserted activities. In this case, as noted above, the function of SEQ ID NO:2 was assigned based solely on sequence similarity and it is just as likely that the polypeptide of SEQ ID NO:2 is a non-functional mutant. Even assuming *arguendo* SEQ ID NO:2 has primase activity, the effects of amino acid substitution on the function of a polypeptide are highly unpredictable as evidenced by Branden et al. and the specification provides no guidance as to which of those amino acids of SEQ ID NO:2 can be altered with an expectation of maintaining primase activity – if at all present – or the ability to bind SEQ ID NO:4. While SEQ ID NO:2, which is within the scope of the claimed polypeptides, can be used to generate antibodies that are useful in the detection of *S. aureus,* it is not clear that variants of the polypeptide of SEQ ID NO:2 would be so useful, particularly in view of the evidence of Abaza et al. and Colman et al.

Applicants request clarification of the following statement, "[a]pplicants have allegedly identified amino acids 561-599 of the *S. aureus* polypeptide of SEQ ID NO:2 as being required for binding of SEQ ID NO:2 to SEQ ID NO:4." In response, it is noted that the term "allegedly" was not appropriately used as the specification discloses data suggesting that SEQ ID NO:6 binds SEQ ID NO:4.

In response to the examiner's argument that the polypeptides of clams 91 and 107-108 are not limited to those that bind SEQ ID NO:4, applicants acknowledge that the scope of these polypeptides is not limited to those polypeptides that bind to SEQ ID NO:4, but is limited to polypeptides having enzymatic activities. Applicants argue the specification discloses assays that are useful in measuring the biological activity of the claimed polypeptides, citing pp. 23-26 and 84-89 of the specification.

Applicants' argument is not found persuasive. Initially, it is noted that the scope of polypeptides of claims 107-108 is not limited to those having enzymatic activity. The specification fails to define "activation of DNA polymerase activity," "stimulation of helicase activity," and "stimulation of ATPase activity" as being enzymatic activities, the prior art does not recognize such activities as being limited to enzymatic activities. Further, as noted above, there is no evidence of record that SEQ ID NO:2 has primase activity. Even assuming SEQ ID NO:2 has primase activity, the polypeptides of claims 86-87, 91, and 107-108 are not limited to polypeptides comprising SEQ ID NO:6 and the specification fails to provide guidance regarding those amino acids that can be altered with an expectation of maintaining primase activity or the ability to bind SEQ ID NO:4.

Applicants argue the skilled artisan can make all polypeptides and screen for those that have the desired activity/utility as no special technical knowledge is required to make and test altered proteins and such experimentation is routine. Applicants argue the specification teaches methods for screening polypeptides having the recited activities.

As previously stated, while methods of altering the sequence of a polypeptide were known in the art at the time of the invention, it was not routine to screen a significant number of variants – as encompassed by the claims – without guidance regarding those amino acids of a polypeptide that can be altered without affecting the desired activity/utility. As stated in a previous Office action, the effects of amino acid substitution on the function of a polypeptide are highly unpredictable and the specification fails to provide any guidance regarding those amino acids of SEQ ID NO:6 that are required for binding to SEQ ID NO:4 or those amino acids of SEQ ID NO:2 that are required for the recited activities of claims 91 and 107-108. As such, one must randomly alter the sequence – within the identity or similarity limitation – to make and screen those polypeptides that have the desired activity/utility. According to the sequence listing, the polypeptide of SEQ ID NO:2 is 599 amino acids in length. A skilled artisan must replace all 599 amino acids of SEQ ID NO:2 with 19 other common amino acids just for *single amino acid substitutions.* Take into consideration that one must perform not only single amino acid substitutions, but also single amino acid additions, deletions, and insertions and multiple amino acid substitutions, additions, deletions, and insertions, and combinations thereof within the percentage identity or similarity limitation

to make the full scope of claimed or recited variants of SEQ ID NO:2. One must then screen all variants for those having the desired activity/utility. While it is acknowledged that a single amino acid substitution in a protein is not likely to disrupt protein activity, the scope of variants is not limited to a single amino acid substitution, but encompasses additions, deletions, and insertions, and combinations of substitutions, additions, deletions, and insertions of a polypeptide that is 599 amino acids in length.

In response to the examiner's argument that the regions of the sequences of SEQ ID NO:2 and 4 involved in binding are likely exposed at their respective surface and that the specification provides no evidence that a polypeptide comprising an internalized SEQ ID NO:6 would bind SEQ ID NO:4, applicants note the examiner has taken "official notice" and argue the location of the binding domain of all proteins would not be a fact of "instant and unquestionable demonstration as to defy dispute." Applicants argue the examiner has provided no evidence in support of such an assertion and, according to applicants, it would not require undue experimentation for a skilled artisan to test a polypeptide's ability to bind a cognate polypeptide in view of the specification's disclosure of such test methods.

Applicants' argument is not found persuasive. First, it is noted that the examiner characterized the binding domains of SEQ ID NO:2 and SEQ ID NO:4 as "likely being exposed at the surface of the polypeptide." Applicants do not dispute the examiner's assertion and instead attack the credibility of the source. MPEP 2144.03 states, "[o]fficial notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common

knowledge in the art are capable of instant and unquestionable demonstration as being well-known." In this case, evidence that the binding domains of SEQ ID NO:2 and SEQ ID NO:4 are "likely [to be] exposed at the surface of the polypeptide" is supported by Charkrabarti et al. (*Proteins* 47:334-343), which states, "[p]rotein-protein recognition depends on the physical and chemical properties of the interfaces that form as two protein surfaces come in contact to form a specific complex" (underline added for emphasis; p. 334, left column, first sentence under "Introduction"). Bogan et al. (*J. Mol Biol* 280:1-9) teaches "[m]ost interfaces [of protein-protein interactions] are composed to two relatively large protein surfaces..." (p. 1, left column, bottom). Also, The "Encyclopedia of Molecular Biology" teaches that it is the complementarity of protein surfaces that allow for their interaction (see pp. 2029-2030). As such, one of skill in the art would recognize the part of SEQ ID NO:2 and the part of SEQ ID NO:4 that interact are likely exposed at the surface of the respective protein. It is again noted that, as stated above, the positioning of SEQ ID NO:6 at the C-terminus of SEQ ID NO:2 appears to be structurally important, particularly as the primase polypeptides of SEQ ID NO:2 and O'Donnell et al. and the primase polypeptide encoded by the nucleic acid of Benton et al. (cited in the Office action mailed 6/1/2004) all have the sequence of SEQ ID NO:6 *at their C-termini.* Further, applicants have presented no objective evidence that placing SEQ ID NO:6 within an amino acid sequence, *e.g.,* SEQ ID NO:6 having 100 additional amino acids at the C-terminal end thereof) maintains binding to SEQ ID NO:4. As noted above, the primary sequence of a polypeptide determines its three-dimensional structure, which in turn determines its ability to bind to other proteins. As

such, it is highly unpredictable as to the effects of burying SEQ ID NO:6 within an amino acid sequence on its ability to maintain binding to SEQ ID NO:4.

In response to the examiner's argument that the effects of amino acid sequence alterations on the function of a polypeptide are highly unpredictable, applicants again argue that undue experimentation is not required to make and use all polypeptides encompassed by the scope of the claims.

Applicants' argument is not found persuasive for reasons already made of record and discussed at length above and in previous Office actions.

In response to the examiner's statement that in making the scope of polypeptides encompassed by the claims one must screen those polypeptides for those that have the ability to inhibit growth of *S. aureus*, applicants argue that none of the claims includes a limitation that the claimed polypeptides must have the ability to inhibit growth of *S. aureus*.

The examiner acknowledges that there is no recited limitation that the polypeptides inhibit growth of *S. aureus*.

Applicants argue the references relied upon by the examiner to establish unpredictability in the art are irrelevant to the instant case as the references concern antibodies and the claims are not drawn to antibodies, but to *S. aureus* polypeptides and fragments and variants thereof, whose structures and activities in other species are well known, according to applicants.

Although not expressly stated, it appears applicants are referring to the references of Abaza et al. and Colman et al. (cited in the Office action mailed

10/28/2004), cited as supporting the high level of unpredictability in altering the amino acid sequence of the binding domain of a protein with an expectation of maintaining binding activity. The examiner acknowledges that the references concern antibody-antigen binding. However, the examiner disagrees with applicants' assertion that the references are irrelevant merely because they are concerned with antibodies. It should be noted that applicants do not dispute the findings of Abaza et al. and Colman et al. The references of Abaza et al. and Colman et al. are relevant because antibody-antigen binding is a protein-protein interaction, evidenced by Buckingham, which teaches "[a]ntibody-antigen binding is a well described protein-protein interaction" (p. 1, left column, middle). See p. 2027, right column, of the "Encyclopedia of Molecular Biology." Similarly, binding between SEQ ID NO:2 or 6 and SEQ ID NO:4 is a protein-protein interaction. As such, one of skill in the art would expect the teachings of Abaza et al. and Colman et al. to be applicable in supporting the unpredictability of altering a first protein binding site with an expectation of maintaining binding between the first protein and a second protein.

Regarding the references of Abaza et al. and Colman et al., applicants further argue these references were published in 1992 and 1996 and do not establish the state of the art at the time of the invention. According to applicants, there has been a "tremendous" increase in knowledge since the publication of these references and applicants argue that using this knowledge one could have assessed and identified modifications that alter binding capacities and primase activity.

Applicants' argument is not found persuasive. It is noted that applicants do not dispute the findings of Abaza et al. and Colman et al. While the examiner acknowledges that advances in the art have taken place since the publication of Abaza et al. and Colman et al., the examiner maintains the position that these references are relevant to the instant situation and establish the high level of unpredictability of altering a first protein binding site with an expectation of maintaining binding between the first protein and a second protein. There is no evidence of record that would support applicants' position that, due to advances in technology, the art is so predictable that guidance regarding the effects of altering a protein sequence on its function need not be provided. If applicants dispute the examiner's position, applicants are requested to provide evidence that advances in technology have rendered the findings of Abaza et al. and Colman et al. obsolete. Applicants are reminded that "arguments of counsel cannot take the place of factually supported objective evidence." See MPEP 2144.08.

At least for the reasons of record and the reasons stated above, undue experimentation is required to make and use the full scope of the claimed invention.

Conclusion

[8] Status of the claims:

- Claims 66, 72, 86-88, 91, and 105-108 are pending.
- Claims 88 and 105-106 appear to be in a condition for allowance.
- Claims 66, 72, 86-87, 91, and 107-108 are rejected.

- Claims 66, 72, 86-87, 91, and 107-108 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 1st paragraph, set forth in this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:30 am to 4:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

03-18-05
DAVID J. STEADMAN, PH.D.
PRIMARY EXAMINER